INVITED PAPER:

A stepwise personalized approach to blood pressure management considering circadian effects and cardiovascular prognosis

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There are significant circadian rhythms in blood pressure (BP). For example, nocturnal BP falls by 10% to 20% of daytime BP (normal dipper pattern). This circadian rhythm is determined partly by the intrinsic rhythm of central and peripheral clock genes, which regulate the neurohumoral factors and cardiovascular systems, but predominantly by the sleep–wake behavioral pattern. Several environmental and behavioral factors and pathological diseases affect this circadian rhythm of BP (Figure 1).[1] Since O'Brian first described the division of nocturnal BP patterns into nondippers (diminished nocturnal BP fall) and dippers,[2] the classification has expanded to include 4 nocturnal BP dipping patterns: the dipper, non-dipper, riser, and extreme dipper patterns.[1] In addition to these circadian patterns, individual 24-hr BP patterns are affected by various shorter-term BP variabilities, such as morning BP surge, physical or psychological stress-induced daytime BP, and night-time BP surges triggered by obstructive sleep apnea (OSA) episodes, arousal, rapid-eye-movement sleep, and nocturnal behaviors (nocturia).

Disrupted circadian patterns, such as non-dipper (reduced nighttime BP fall) and riser (higher nighttime BP than daytime BP) patterns, have been well-established to confer risk for cardiovascular disease (CVD) events and organ damage in both community-dwelling subjects and hypertensive patients.[1] In addition, we first described extreme-dippers with excessive nocturnal BP fall as an additional pathological pattern of disrupted circadian rhythm, with advanced silent cerebral disease (silent cerebral infarct and white matter disease) demonstrated by brain MRI, and with increased prognostic risk of subsequent clinically overt stroke events based on a prospective study of elderly hypertensive patients.[3,4] A recent meta-analysis demonstrated that an extreme-dipper pattern is associated with incidence of CVD risk in very elderly patients.[5]

Antihypertensive medications that affect circadian BP variation might modify the CVD prognosis. A recent clinical trial showed the marked benefit of bedtime dosing of antihypertensive drugs compared with waking dosing on the cardiovascular prognosis in hypertensive patients.[6] In this study, the CVD events were markedly reduced by 56% for CVD death, 34% for myocardial infarction, 42% for heart failure, and 49% for stroke in the bedtime-dosing arm when compared with the wakening-dosing arm, even after controlling for nighttime BP and nighttime BP falls. There are several points worth discussing in regard to this study. First, the degree of risk reduction of CVD events was much higher than expected from the previous evidence. These benefits of CVD event reduction correspond to an office BP reduction of approximately 20 mmHg systolic and 10 mmHg diastolic according to the results of a systematic review of previous randomized controlled trials of antihypertensive drugs.[7] The impact of nocturnal hypertension is greater in medicated hypertensive patients than in the unmedicated patients, suggesting that a significant number of cases of uncontrolled nocturnal hypertension even among patients with well-controlled daytime BP by conventional office BP-guided antihypertensive approach. As estimated from the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO), a 50% difference of CVD events corresponds to a 40 mmHg difference in nighttime BP in medicated patients.[8] However, in a recent clinical cross-over trial of evening (6 pm-11 pm) vs morning (6 am-11 am) dosing among hypertensive patients with reasonably well-controlled BP, the timing of antihypertensive drug administration (morning or evening) did not affect mean 24-hr or

office BP levels.[9] What mechanisms of non-specific bedtime dosing contribute to such a marked benefit without difference in the nighttime BP level or nocturnal dipping status? In consideration of these disparate results, any standardized change in the dosing of all antihypertensive drugs from morning to bedtime for all hypertensive patients should wait until the results of future clinical trials.

Instead, I would like propose a STEpwise-Personalized 24-hr approach (STEP24 approach) for the management of hypertension, targeting morning BP first and nighttime BP second (***Figure 2***) to achieve perfect 24-hr BP control than the standardized bedtime dosing to achieve perfect 24-hr BP control in clinical practice. To reduce morning BP effectively, long-acting antihypertensive drugs should be considered a first step, and if morning BP is not controlled, then bedtime-dosing or twice-daily dosing of antihypertensive medication might be a second step. After controlling morning BP, uncontrolled nocturnal hypertension would seem to be the next logical target. Conventionally, nighttime BP has been measured by ambulatory BP monitoring in clinical practice. Recently, we demonstrated that nocturnal hypertension evaluated by home BP monitoring was associated with poor prognosis of stroke and coronary artery disease events in the J-HOP (Japan Morning Surge-Home Blood Pressure) Nocturnal BP study.[10] Thus, nocturnal home BP measurement could be useful for the STEP24 approach in clinical practice.

Theoretically, several different approaches involving pressor mechanisms could be used to control nocturnal BP effectively (***Figure 2***).[1] The effectiveness of these approaches should be tested in future clinical studies. For example, for salt-sensitive non-dippers with increased circulating volume, salt restriction, diuretics, and new drugs such as a sodium-glucose cotransporter 2 inhibitor (SGLT2i) and angiotensin receptor neprilysin inhibitor (ARNi)seem to be effective. Calcium channel blockers would be preferable for patients with structural nocturnal hypertension with vascular remodeling of the small and large arteries. For patients with sympathetic hyperactivity exhibiting nocturnal and morning hypertension, renal denervation and bedtime dosing of sympatholytic drugs such as doxazosin and carvedilol are effective to suppress the nighttime BP and morning and sleep BP surges.

To achieve perfect BP control in consideration of the different circadian BP variabilities, a personalized approach would essentially be the best method on the top of guideline-driven standardized approach, to minimize the CVD event risk. Given the marked and continuing advances in information and communication technology, a personalized approach based on the 24-hr BP profile accurately and frequently measured by a wearable BP-monitoring device could be expected to dramatically change the quality of hypertension management in the near future.

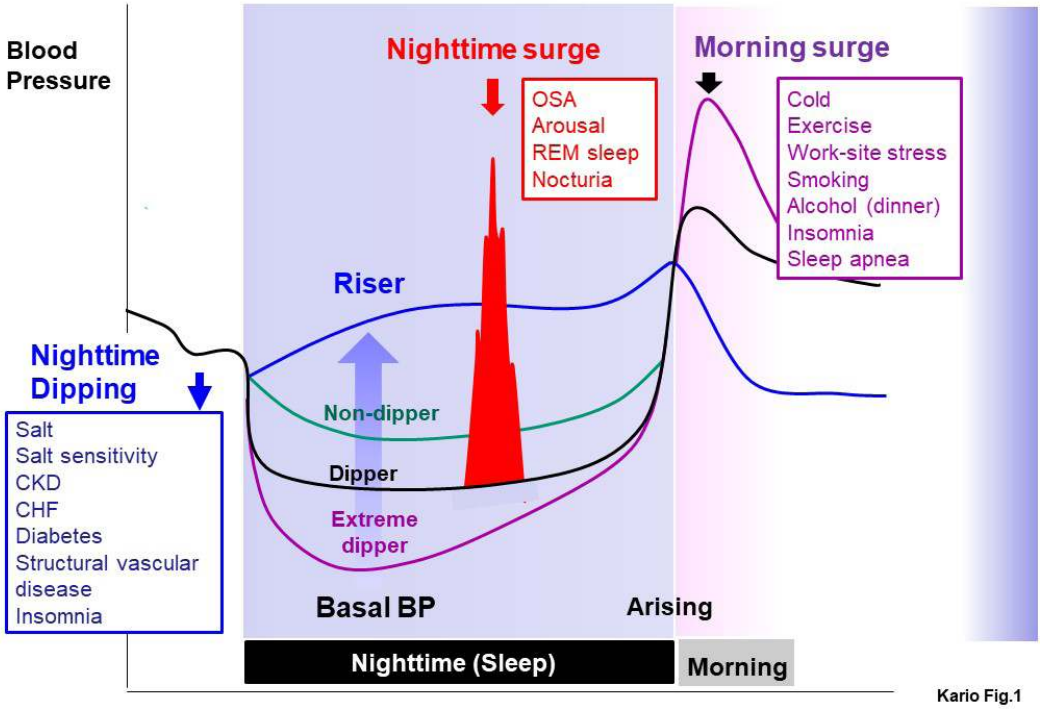

Figure 1. Components of nocturnal hypertension and determinants – nighttime dipping status and surge in blood pressure. CKD, chronic kidney disease; CHF, chronic heart failure; BP, blood pressure; REM, rapid eye movement. [1]

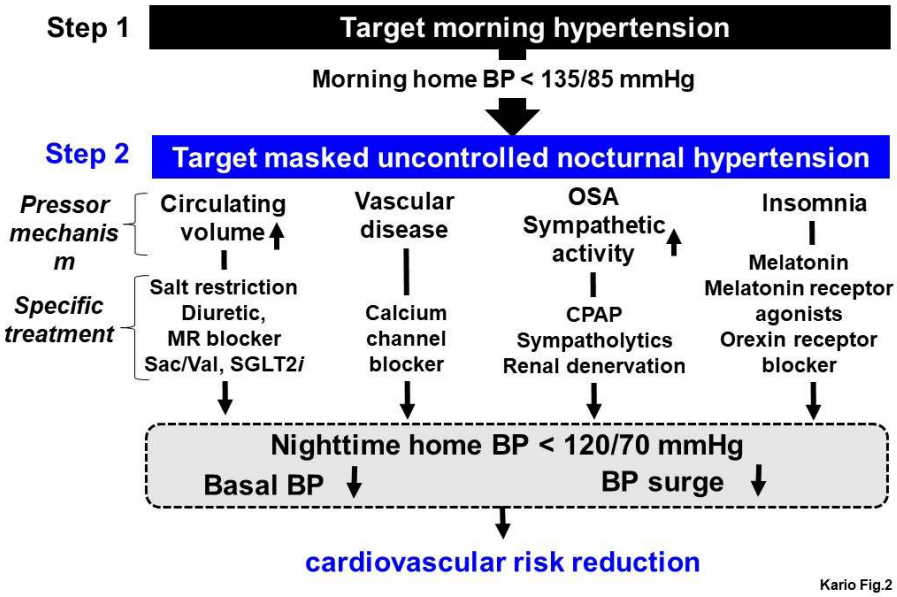

Figure 2. STEpwise-Personalized 24-hr blood pressure control approach (STEP24 approach) BP, blood pressure; MR, mineralocorticoid receptor; Sac/val, sacubitril/valsartan; SGLT2i, sodium glucose cotransporter 2 inhibitor; OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure. [1]

Kario Fig.2

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